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☐ 1. Document ID: US 6159505 A

L5: Entry 1 of 2 File: USPT

US-PAT-NO: 6159505
DOCUMENT-IDENTIFIER: US 6159505 A

TITLE: Compositions for the treatment of migraine, containing potassium, magnesium and pyridoxine

DATE-ISSUED: December 12, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Piper; Edwina M.	By Leven, Fife			GB

US-CL-CURRENT: 424/679; 424/466, 424/601, 424/602, 424/630, 424/637, 424/639, 424/641, 424/646, 424/665, 424/670, 424/682, 424/683, 424/686, 424/688, 424/689, 424/692, 424/697, 424/717, 424/722, 424/725, 514/165, 514/249, 514/251, 514/276, 514/345, 514/355, 514/387, 514/419, 514/456, 514/457, 514/458, 514/464, 514/474, 514/52, 514/563, 514/570, 514/574, 514/629, 514/630, 514/904, 514/905

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

☐ 2. Document ID: US 6130244 A

L5: Entry 2 of 2 File: USPT

US-PAT-NO: 6130244
DOCUMENT-IDENTIFIER: US 6130244 A

TITLE: Product and method to reduce stress induced immune suppression

DATE-ISSUED: October 10, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Wood; Steven M.	Pickerington	OH		

US-CL-CURRENT: 514/474; 424/600, 424/630, 424/638, 424/641, 424/643, 424/702, 424/725, 514/12, 514/168, 514/2, 514/23, 514/249, 514/400, 514/419, 514/423, 514/458, 514/494, 514/499, 514/500, 514/52, 514/54, 514/546, 514/547, 514/549, 514/552, 514/556, 514/558, 514/561, 514/562, 514/564, 514/565, 514/567, 514/7, 514/706, 514/725, 514/763, 514/786, 514/904, 514/905

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Draw. Desc | Image

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Term	Documents
(3 AND 1 AND 2).USPT,PGPB.	2
(L3 AND L2 AND L1).USPT,PGPB.	2

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09/815 566

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L2: Entry 3 of 3 File: USPT Oct 19, 1999

US-PAT-NO: 5968896
DOCUMENT-IDENTIFIER: US 5968896 A

TITLE: Nutritional supplement for preoperative feeding

DATE-ISSUED: October 19, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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APPL-NO: 09/ 008156 [PALM]
DATE FILED: January 16, 1998

INT-CL: [06] A61 K 38/00, A61 K 31/70, A61 K 31/715, A61 K 31/595

US-CL-ISSUED: 514/2; 514/23, 514/53, 514/54, 514/59, 514/60, 514/546, 514/547, 514/558, 514/560, 514/168, 514/458, 514/474
US-CL-CURRENT: 514/2; 514/168, 514/23, 514/458, 514/474, 514/53, 514/54, 514/546, 514/547, 514/558, 514/560, 514/59, 514/60

FIELD-OF-SEARCH: 514/2, 514/23, 514/53, 514/54, 514/59, 514/60, 514/546, 514/547, 514/558, 514/560, 514/168, 514/458, 514/474

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4981844	January 1991	Alexander et al.	514/21
☐	5234702	August 1993	Katz et al.	426/72
☐	5308832	May 1994	Garleb et al.	514/2
☐	5605893	February 1997	Kaufman	514/60
☐	5821217	October 1998	Forse et al.	514/2
☐	5843921	December 1998	Kaufman	514/60

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0183305	June 1986	EP	
WO 91/18610	December 1991	WO	

OTHER PUBLICATIONS

Fan, S.T., et al., "Perioperative Nutritional Support in Patients Undergoing Hepatectomy for Hepatocellular Carcinoma," The New England Journal of Medicine, 331 (23) : 1547-1552 (Dec. 8, 1994).
Hirai, Y., et al., "An Enteral Elemental Diet for Infants and Children with Surgical Disorders," Journal of Parenteral and Enteral Nutrition, 4: 460-463 (Sep.-Oct. 1980).
Glotzer, D.J., et al., "Preoperative Preparation of the Colon with an Elemental Diet," Surgery, 74(5) : 703-707 (Nov. 1973).

ART-UNIT: 164

PRIMARY-EXAMINER: Weddington; Kevin E.

ATTY-AGENT-FIRM: Hamilton, Brook, Smith & Reynolds, P.C.

ABSTRACT:

A nutritional supplement is described comprising approximately from about 10 to about 75 grams carbohydrate; approximately from about 5 to about 50 grams protein; approximately from about 3 to about 30 grams fat; and therapeutic amount of antioxidant, for use in weight maintenance in individuals who will undergo major surgery to prevent or reduce postoperative complications.

30 Claims, 0 Drawing figures
Exemplary Claim Number: 1

BRIEF SUMMARY:

1 BACKGROUND

2 Postoperative complications, including infections at a surgical site and other distant nosocomial infections in high risk patients, are estimated to be between 25% and 30%. Patients particularly prone to postoperative infections are those who are malnourished prior to surgery, the elderly, and those about to undergo major gastrointestinal and non-cardiac thoracic procedures.

3 As early as 1987, perioperative use of parenteral nutrition was recommended by the Health and Public Policy Committee of the American College of Physicians for severely malnourished patients having major surgery, such as intra-abdominal or non-cardiac intrathoracic surgery (Health and Public Policy Committee, American College of Physicians, "perioperative parenteral Nutrition", Ann. Int. Med., 107:252-253 (1987)). Unselected use of total parenteral nutrition (TPN) is not justified, especially in mild or moderately malnourished patients because its use has been shown to be associated with an increased rate of infections and non-infectious complications (Detsky et al., "Perioperative Parenteral Nutrition: A Meta-Analysis", Ann. Int. Med., 187;107:195-203) . Around the same time, Klein and others (Klein et al., "Total Parenteral Nutrition and Cancer Clinical Trials", Cancer, 58:1378-1386 (1986).) reviewed the existing literature on cancer patients and found that the TPN is not useful if used routinely in all patients with cancer. However, they found that its preoperative use in cancer patients with gastrointestinal disease may help reduce major surgical complications and improve survival, treatment toxicity, and tumor response in patients receiving chemotherapy or radiation therapy.

4 Recently, thirty-three, high quality, randomized, prospective studies were reviewed on the subject of pre- and post-operative feeding, including 2,500 patients (Klein et al., "Nutritional Support in Clinical Practice: Review of Published data and recommendations for Future Research Directions", J. Parent. Ent. Nutr., 21: 133-156 (1997)). There were 13 studies including 1,250 patients who received preoperative TPN for 7 to 10 days. Most of the studies (9/13) found that patients, who received TPN and were moderately malnourished based on weight loss or depressed serum protein concentrations, had fewer postoperative complications. Those receiving preoperative TPN had 10% fewer complications and no change in mortality rates compared to those who were not preoperatively fed. There were two studies where enteral nutrition was used preoperatively for 10 days in cancer patients and postoperative complications were reduced (12%).

5 SUMMARY OF THE INVENTION

6 The invention pertains to a nutritional supplement for enteral administration which provides optimal nutrition for weight maintenance in individuals who will undergo major surgery, to provide nutrition which may reduce postoperative complications of surgery. Methods of administering the nutritional supplement to preoperative patients are described. The nutritional supplement can improve the nutritional status of the patient when administered for a period of time prior to surgery, to prepare the patient's body for major surgery through nutrition, and to improve defense capacity against postoperative infections are also described. An advantage of the methods and nutritional supplement is to provide a source of calories and protein to the patient prior to surgery to address malnourishment and to prevent further weight loss.

7 The nutritional supplement contains approximately from about 10 to about 75 grams carbohydrate; approximately from about 5 to about 50 grams protein; approximately from about 3 to about 30 grams fat comprising at least two different fat sources of which one is oil rich in monounsaturated fatty acids and the other is oil rich in omega-3 fatty acids; and antioxidant(s). In a preferred embodiment of the invention, the nutritional supplement contains from about 20% to about 40% of calories derived from protein; from about 25% to about 45% of calories derived from carbohydrate; and from about 26% to about 46% of calories derived from fat. The percentages are selected so as to add to 100%.

8 The carbohydrate can include one or more sources of carbohydrate, such as corn syrup, high fructose corn syrup, corn starch, maltodextrin, fructose, lactose, glucose,sucrose, dextrose, maltose and combinations thereof. The protein can include one or more sources of protein, such as whey protein, whey protein concentrate, whey powder, egg protein, soy protein, soy protein isolate, caseinate and combinations thereof. The fat can include one or more sources of fat, including dairy fat, coconut oil, fish oil and/or vegetable oil. Fat can be included in its natural triglyceride state as long-, medium- or short-chain triglycerides, or as structured triglycerides comprised of long-, medium- or short-chain triglycerides.

9 The nutritional supplement can be provided in a variety of forms, such as baked goods, puddings, confections, snack foods, ice cream, frozen confections and novelties, or non-baked, extruded foods such as bars. The nutritional supplement of the invention can be daily administered to preoperative patients to prepare them for surgery to improve nutritional status which may prevent or minimize the risks of postoperative complications. The composition is particularly suitable for use in patients who suffer from depressed host defence mechanisms, e.g. in patients who suffer from depressed host defence mechanisms as a result of post-surgical stress, cancer, chemotherapy/radiation therapy, sepsis, immunosuppressive drug therapy, HIV infection and malnutrition.

DETAILED DESCRIPTION:

1 DETAILED DESCRIPTION OF THE INVENTION

2 The invention is drawn to a nutritional supplement that provides nutritional support (herein referred to as a "nutritional supplement") for individuals preparing for an imminent major surgical procedure, and to methods for administration of the nutritional supplement. The nutritional supplement is rich in calories and contains ingredients that have been shown to enhance/stimulate immune function. If consumed as part of a daily regimen prior to surgery, malnutrition can be addressed but not fully treated and the possible incidence of postoperative infections may be mitigated. The nutritional supplements of the invention are ideal for patients who are about to undergo major gastrointestinal or non-cardiac thoracic surgery, due to the high post-operative incidence or risk of infection.

3 The nutritional supplement can be made in a variety of forms, such as baked goods (e.g., cookies, brownies, fudge, cake, breads, biscuits, crackers), puddings, confections (i.e., candy), snack foods (e.g., pretzels, chips), ice cream, frozen confections and novelties, or non-baked, extruded food products such as bars. The preferred form is a non-baked extruded nutritional bar.

4 The nutritional supplement includes the following components: from about 10 to about 75 grams carbohydrates; from about 5 to about 50 grams protein; from about 3 to about 30 grams fat comprising at least two different fat sources of which one is oil rich in monounsaturated fatty acids and the other is oil rich in omega-3 fatty acids; and antioxidant(s). The nutritional supplement should provide a balance between total calories and glucose calories to avoid the possibility of inducing hyperglycemia; a complication which may increase infection rate.

5 In a preferred embodiment, the nutritional supplement comprises from about 10 to about 25 g carbohydrate; from about 10 to about 25 g protein; from about 5 to about 15 g fat; and about one half RDA amounts of antioxidants selected from the group consisting of vitamin A (as vitamin A and .beta.-carotene), vitamin C, vitamin E and combinations thereof. In another embodiment, the amount of vitamin A is from about 250 .mu.g to about 750 .mu.g; the amount of .beta.-carotene is from about 2000 .mu.g to about 4000 .mu.g; the amount of vitamin C is from about 25 mg to about 65 mg (60 mg=RDA); and the amount of vitamin E is from about 5 mg to about 30 (30 mg=RDA).

6 Preferably, the percentages of calories in the serving unit are derived from the following sources: protein, from about 20% to about 40%; carbohydrate, from about 25% to about 45%; and fat, from about 26% to about 46%. For purposes of this invention, a preferred nutritional supplement comprises the components described above as a single serving (serving unit), whereby one or a plurality of these supplement(s) is consumed daily. Alternatively, the serving unit can represent the total daily allowance of the components that comprise the nutritional supplement, for example as having the percentages defined above. The RDA amounts of antioxidants will vary depending upon the number or servings administered daily to the patient. This amount will also be dictated, in part, by patient condition.

7 It should be understood that the term "carbohydrate" generally includes simple carbohydrates (i.e., monosaccharides and disaccharides) and complex carbohydrates (i.e., polysaccharides). Sources of carbohydrate can include corn syrup, high fructose corn syrup, corn starch, uncooked corn starch, high amylose starch (e.g., such as those derived from but not limited to peas, barley, corn, potato, wheat, rice, tapioca, cassava, arrowroot, sage and oat), maltodextrin, fructose, lactose, sucrose, glucose, dextrose, syrups (e.g., maltitol), maltose and combinations of these. In a preferred embodiment, the nutritional supplement contains a variety of carbohydrate sources, each source selected from a different glycemic index (see Modern Nutrition in Health and Disease, eighth edition, Lea & Febiger, publishers, 1986, especially Volume 2, page 1270 and Appendix page A-135), so that glucose is released sequentially into the blood as the nutritional supplement is digested and absorbed. In a preferred embodiment, a nutritional supplement would contain carbohydrate having a low glycemic index (e.g., from less than about 70), intermediate glycemic index (e.g., from about 70 to about 80), high glycemic index (e.g., from greater than about 90) and

combinations of these. Ibid. For example, the nutritional supplement can contain sucrose, which appears in the blood first; high fructose corn syrup, such as high fructose corn syrup comprising about 42% fructose and about 43% glucose, which appears next; corn syrup, which comprises glucose polymers and appears next; and uncooked corn starch, which is slowest to release into the blood and lasts up to 8 hours in the blood (i.e., having the lowest glycemic index). See Kaufman et al., U.S. Pat. No. 5,605,893 and U.S. Ser. No. 08/631,584. In another embodiment, the carbohydrate is a mixture of sucrose, maltodextrin and uncooked corn starch. Sucrose is the preferred simple carbohydrate (i.e., high glycemic index) because it provides the most desirable organoleptic properties compared to other sweeteners. Uncooked cornstarch is a preferred complex carbohydrate having a low glycemic index but should be included in food/beverage formulations which are not cooked or heat processed since the heat will break down the complex carbohydrate into simple carbohydrate (single glucose constituents), creating a high glycemic index product.

8 Staggering the release of sugars into the body prevents too much of an exacerbation of catecholamine excretion occurring immediately after ingestion of the nutritional supplement. A sudden burst of catecholamine may depress appetite even further. In addition, using carbohydrates that are bound to other glucose molecules in high glycemic index foods (i.e., using polysaccharides instead of solely mono- or disaccharides), it is possible to avoid raising insulin levels too quickly or too high which would in turn decrease free fatty acids, which increase serum tryptophan which, in turn, fosters an increase in the level of the brain neurotransmitter serotonin. This is particularly desirable because an increase in the brain serotonin level decreases appetite. This would exacerbate suppression of appetite. Staggering release of sugars also avoids the risk of hyperglycemia which is shown to increase the risk of infection in patients receiving total parenteral nutrition.

9 Sources of protein can be any suitable protein utilized in nutritional formulations and can include whey protein, whey protein concentrate, whey powder, egg, soy protein, soy protein isolate, caseinate (e.g., sodium caseinate, sodium calcium caseinate, calcium caseinate, potassium caseinate), animal and vegetable protein and mixtures thereof. When choosing a protein source, the biological value of the protein should be considered first, with the highest biological values being found in caseinate, whey, lactalbumen, egg albumen and whole egg proteins. In one embodiment, the protein source is whey protein. In another embodiment, the protein is a combination of whey protein concentrate and calcium caseinate, because these proteins have high biological value, that is, they have a high amount of the essential amino acid that is in least concentration relative to the needs of the individual. See Modern Nutrition in Health and Disease, eighth edition, Lea & Febiger, publishers, 1986, especially Volume 1, pages 30-32 .

10 Fats and oils include but are not limited to dairy fat (e.g., butter); vegetable oil, such as canola oil, corn oil, soybean oil, sesame seed oil, safflower oil, sunflower oil, walnut oil, evening primrose oil, peanut oil, cottonseed oil, high oleic sunflower oil, rapeseed oil, olive oil, fish oil (e.g., menhaden oil, sardine oil) and mixtures thereof, all of which are examples of long-chain triglycerides; coconut oil, macadamia oil, palm oil, palm kernel oil, or mixtures thereof, all of which are examples of medium-chain triglycerides. Medium-chain triglycerides are rapidly taken up and used by the body (see, e.g., U.S. Pat. No. 4,871,768 of Bistrian et al. for examples of suitable fat sources; the entire teachings are incorporated herein by reference). The oils can be used in their natural states; alternatively, structured triglycerides, which can be either randomly re-esterified or specifically reesterified, can be generated from two or more oils and used as a fat source. Structured triglycerides can contain long-chain triglycerides, medium-chain triglycerides, short-chain, triglycerides, or combinations thereof. In a preferred embodiment, the source of fat is canola oil. See U.S. Pat. No. 5,260,336 to Forse and Mascioli and Yaqoob et al., Am J. Clin. Nutr., 67:129-35 (1998) for examples of monounsaturated fats; the entire teachings of which are incorporated herein by reference.

11 Fats are the most calorically dense nutrient; however, fat calories, and

particularly longer chain fats or more saturated fats, are typically the poorest absorbed, compared to protein and carbohydrate calories (Modern Nutrition in Health and Disease, eighth edition, Lea & Febiger, publishers, 1986, especially Volume 1, pages 82-83) . In order for weight gain to occur, calories need to be absorbed. Thus, in one embodiment, the fat includes fish oil, butter, canola oil and structured triglycerides, which have been shown to be well absorbed in critically ill patients who have difficulty absorbing fats (Kenler, A.S. et al., Annals of Surg., 223(3):316-333 (1996); Christensen et al., Am. J. Clin. Nutr., 61:56-61 (1995)).

12 Preferably, the nutritional supplement provides approximately 200 kcal per unit serving, because it is designed to supplement regular meals, rather than to replace them. The objective of the invention is to supplement the diet of an individual, and not to depress the individual's appetite at meals themselves; the 200 kcal size is optimal to meet this objective. Further, a nutritional bar that provides 200 kcal per serving makes it easy for the individual and/or health care provider to track calories. However, other unit serving sizes are embraced by the invention, e.g. from about 100 to about 300 kcal/serving.

13 The nutritional supplement comprises one or a combination of antioxidants in therapeutic amounts. Antioxidants suitable for use in this invention include, but are not limited to, vitamin A, vitamin C, vitamin E, .beta.-carotene, zinc, chromium, selenium and herbs, such as ginkgo biloba, ginsing. A "therapeutic amount" is intended herein to be an amount which is sufficient to provide a therapeutic benefit to the patient. The amount of antioxidant(s) per unit serving are a matter of design and will depend upon the total number of unit servings of the nutritional supplement daily administered to the patient. The total amount of antioxidant(s) will also depend, in part, upon the condition of the patient. Preferably the amount of antioxidant(s) will be a fraction or multiplier of the RDA amounts. For example, the nutritional supplement will comprise 50% RDA antioxidants per unit dosage and the patient will consume two units per day.

14 It is desirable to daily administer the nutritional supplement from about seven to about ten days prior to surgery in moderately to severely malnourished patients. Patients who tend to be malnourished or undernourished, include, but are not limited to, those suffering from post surgical stress, cancer, chemotherapy/radiation therapy, sepsis, immunosuppressive drug therapy, HIV infection and malnutrition. The nutritional supplements of this invention can be used alone or in combination with parenteral nutritional, enteral nutritional supplements consumed orally or administered by tube, or regular diet.

15 The nutritional supplement can also contain other ingredients such as one or a combination of other vitamins, minerals, antioxidants, fiber and other dietary supplements. Selection of one or several of these ingredients is a matter of formulation design, consumer preference and end-user. The amount of these ingredients added to the nutritional supplements of this invention are readily known to the skilled artisan and guidance to such amounts can be provided by the U.S. RDA doses for children and adults. Vitamins and minerals that can be added include, but are not limited to, calcium phosphate or acetate, tribasic; potassium phosphate, dibasic; magnesium sulfate or oxide; salt (sodium chloride); potassium chloride or acetate; ascorbic acid; ferric orthophosphate; niacinamide; zinc sulfate or oxide; calcium pantothenate; copper gluconate; riboflavin; beta-carotene; pyridoxine hydrochloride; thiamin mononitrate; folic acid; biotin; chromium chloride or picolonate; potassium iodide; sodium selenate; sodium molybdate; phylloquinone; Vitamin D.sub.3 ; cyanocobalamin; sodium selenite; copper sulfate; Vitamin A; Vitamin E; Vitamin B.sub.6 and hydrochloride thereof; Vitamin C; inositol; Vitamin B.sub.12 ; potassium iodide.

16 Flavors, coloring agents, spices, nuts and the like can be incorporated into the product. Flavorings can be in the form of flavored extracts, volatile oils, chocolate flavorings, peanut butter flavoring, cookie crumbs, crisp rice, vanilla or any commercially available flavoring. Examples of useful flavorings include but are not limited to pure anise extract, imitation banana extract, imitation cherry extract, chocolate extract, pure lemon extract, pure orange

extract, pure peppermint extract, imitation pineapple extract, imitation rum extract, imitation strawberry extract, or pure vanilla extract; or volatile oils, such as balm oil, bay oil, bergamot oil, cedarwood oil, cherry oil, walnut oil, cinnamon oil, clove oil, or peppermint oil; peanut butter, chocolate flavoring, vanilla cookie crumb, butterscotch or toffee. In a preferred embodiment, the nutritional supplement contains cocoa or chocolate.

17 Emulsifiers may be added for stability of the final product. Examples of suitable emulsifiers include, but are not limited to, lecithin (e.g., from egg or soy), and/or mono- and di-glycerides. Other emulsifiers are readily apparent to the skilled artisan and selection of suitable emulsifier(s) will depend, in part, upon the formulation and final product.

18 Preservatives may also be added to the nutritional supplement to extend product shelf life. Preferably, preservatives such as potassium sorbate, sodium sorbate, potassium benzoate, sodium benzoate or calcium disodium EDTA are used.

19 In addition to the carbohydrates described above, the nutritional supplement can contain artificial sweeteners, e.g., saccharides, cyclamates, aspartamine, aspartame, acesulfame K, and/or sorbitol. Such artificial sweeteners can be desirable if the nutritional supplement is intended for an overweight or obese individual, or an individual with type II diabetes who is prone to hyperglycemia.

20 In one embodiment, the nutritional supplement is a nonbaked, extruded food bar that provides 200 kcal/unit serving and has the following characteristics:

21 about 17 grams carbohydrate from sucrose, maltodextrin and uncooked corn starch;

22 about 15 grams protein from whey;

23 about 8 grams fat comprising fish oil, butter, canola oil and MCT oil as a structured lipid or physical mixture; and

24 about 50 percent RDA of antioxidants selected from the group consisting of vitamin A (comprising about 50 .mu.g vitamin A and about 3000 .mu.g .beta.-carotene), vitamin C (about 60 mg), vitamin E (about 10 mg as alpha-tocopheryl acetate).

25 To manufacture such a food bar, the liquid ingredients are cooked; the dry ingredients are added with the liquid ingredients in a mixer and mixed until the dough phase is reached; the dough is put into an extruder, and extruded; the extruded dough is cut into appropriate lengths; and the product is cooled.

26 For manufacture of other foods or beverages, the ingredients comprising the nutritional supplement of this invention can be added to traditional formulations or they can be used to replace traditional ingredients, particularly the carbohydrate components. Those skilled in food formulating will be able to design appropriate foods/beverages with the objective of this invention in mind.

27 The nutritional supplement can be consumed at any time of day, as part of a meal or caloric supplementation program. The nutritional supplement is intended to be administered up to two weeks prior to surgery, from about 7 to about 10 days being preferred and two weeks being optional. See also USSN 08/966,829, filed Nov. 10, 1997, the teachings of which are incorporated herein by reference in their entirety, which teaches nutritional supplements that can be used by individuals who are affected by a disease or condition that prevents intake of adequate nutrition or who require increased calories and/or protein.

28 EQUIVALENTS

29 While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without

departing from the spirit and scope of the invention as defined by the appended claims. Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described specifically herein. Such equivalents are intended to be encompassed in the scope of the claims.

CLAIMS:

What is claimed is:

1. A nutritional supplement comprising approximately from about 10 to about 75 grams carbohydrate; approximately from about 5 to about 50 grams protein; and approximately from about 3 to about 30 grams fat comprising at least two different fat sources of which one is oil rich in monounsaturated fatty acids and the other is oil rich in omega-3 fatty acids; and therapeutic amount of antioxidant.

2. The nutritional supplement of claim 1 wherein the supplement comprises from about 10 to about 25 grams carbohydrate.

3. The nutritional supplement of claim 1 wherein the supplement comprises from about 10 to about 25 grams protein.

4. The nutritional supplement of claim 1 wherein the supplement comprises from about 5 to about 15 grams fats.

5. The nutritional supplement of claim 1, the carbohydrate comprises carbohydrate having a high glycemic index; carbohydrate having an intermediate glycemic index; and carbohydrate having a low glycemic index.

6. The nutritional supplement of claim 1, wherein the carbohydrate comprises at least one carbohydrate source selected from the group consisting of: corn syrup, high fructose corn syrup, corn starch, uncooked corn starch, high amylose starch, maltodextrin, sucrose, fructose, lactose, glucose, dextrose, maltose and combinations thereof.

7. The nutritional supplement of claim 1, wherein the carbohydrate comprises more than one carbohydrate source, each carbohydrate source being selected from the group consisting of: corn syrup, high fructose corn syrup, corn starch, uncooked corn starch, high amylose starch, maltodextrin, fructose, sucrose, lactose, glucose, dextrose, maltose and combinations thereof.

8. The nutritional supplement of claim 7, wherein the carbohydrate comprises sucrose, maltodextrin and uncooked corn starch.

9. The nutritional supplement of claim 1, wherein the protein comprises at least one protein source selected from the group consisting of: whey protein, whey protein concentrate, whey powder, egg protein, soy protein, soy protein isolate, sodium caseinate, sodium calcium caseinate, calcium caseinate, potassium caseinate and combinations thereof.

10. The nutritional supplement of claim 1, wherein the protein comprises more than one protein source, each protein source being selected from the group consisting of: whey protein, whey protein concentrate, whey powder, egg protein, soy protein, soy protein isolate, sodium caseinate, sodium calcium caseinate, calcium caseinate, potassium caseinate and combinations thereof.

11. The nutritional supplement of claim 10, wherein the protein source is whey protein.

12. The nutritional supplement of claim 1, wherein the fat is selected from the group consisting of: dairy fat, structured triglycerides, long-chain triglycerides, medium-chain triglycerides, short-chain triglycerides, canola oil, corn oil, soybean oil, sesame seed oil, safflower oil, sunflower oil, high oleic sunflower oil, rapeseed oil, olive oil, sardine oil, walnut oil, menhaden

oil, evening primrose oil, peanut oil, cottonseed oil, coconut oil, macadamia oil, palm oil, palm kernel oil and combination thereof.

13. The nutritional supplement of claim 12, wherein the fat comprises canola oil, fish oil, vegetable oil, dairy fat and medium-chain triglycerides.

14. The nutritional supplement of claim 1, wherein the antioxidant is selected from the group consisting of vitamin A, vitamin E, vitamin C, selenium, herbs and combination thereof.

15. The nutritional supplement of claim 1, wherein the form of the nutritional supplement is selected from the group consisting of: nutritional beverage, baked good, pudding, confection, snack food, ice cream, frozen confection, and non-baked, extruded food product.

16. The nutritional supplement of claim 15, wherein the non-baked, extruded food product is a bar.

17. A nutritional supplement of claim 1 having approximately 200 kcals.

18. A nutritional supplement comprising: approximately from about 10 to about 75 grams carbohydrate, wherein the carbohydrate comprises at least one carbohydrate source selected from the group consisting of: corn syrup, high fructose corn syrup, corn starch, uncooked corn starch, high amylose starch, maltodextrin, sucrose, fructose, lactose, glucose, dextrose, maltose and combination thereof;

approximately from about 5 to about 50 grams protein, wherein the protein comprises at least one protein source selected from the group consisting of: whey protein, whey protein concentrate, whey powder, egg protein, soy protein, soy protein isolate, sodium caseinate, sodium calcium caseinate, calcium caseinate, potassium caseinate and combination thereof;

approximately from about 3 to about 30 grams fat, wherein the fat comprising at least two different fat sources of which one is oil rich in monounsaturated fatty acids and the other is oil rich in omega-3 fatty acids and is selected from the group consisting of: dairy fat, structured triglycerides, long-chain triglycerides, medium-chain triglycerides, canola oil, corn oil, soybean oil, sesame seed oil, safflower oil, sunflower oil, high oleic sunflower oil, rapeseed oil, olive oil, menhaden oil, sardine oil, evening primrose oil, peanut oil, cottonseed oil, coconut oil, macadamia oil, palm oil, palm kernel oil and combinations thereof; and therapeutic amount of antioxidants selected from the group consisting of vitamin A, vitamin C, vitamin E and combinations thereof.

19. The nutritional supplement of claim 18, wherein the carbohydrate comprises sucrose, maltodextrin and uncooked corn starch; wherein the protein source comprises whey protein wherein the fat comprises canola oil, dairy fat, medium-chain triglycerides and fish oil as the source of omega-3 fatty acid; and the antioxidants are vitamin A, vitamin C and vitamin E.

20. The nutritional supplement of claim 19, which is a non-baked, extruded food product.

21. A nutritional supplement comprising approximately from about 10 to about 25 grams carbohydrate; approximately from about 10 to about 25 grams protein; approximately from about 5 to about 15 grams fat; approximately from about 250 .mu.g to about 750 .mu.g vitamin A; approximately from about 2000 .mu.g to about 4000 .mu.g .beta.-carotene; approximately from about 25 mg to about 65 mg vitamin C; and approximately from about 5 mg to about 30 mg vitamin E.

22. An extruded, nonbaked food bar comprising from about 10 to about 75 grams carbohydrate; approximately from about 5 to about 50 grams protein; approximately from about 3 to 30 grams fat comprising at least two different fat sources of which one is oil rich in monounsaturated fatty acids and the other is oil rich in omega-3 fatty acids; and therapeutic amount of antioxidant.

23. The food bar of claim 22 wherein the carbohydrate is from about 10 to about 25 grams; the protein is from about 10 to about 25 grams; the fat is from about 5 to about 15 grams; and about 50% RDA each of vitamin A, vitamin C and vitamin E.

24. The food bar of claim 22 having approximately 200 calories.

25. The food bar of claim 24 comprising sucrose, maltodextrin, corn starch, canola oil, whey protein, fish oil, vegetable oil, dairy fat and medium-chain triglycerides.

26. A method of providing nutritional supplementation to a preoperative patient, comprising administering to the patient, for a sufficient period of time prior to surgery, a nutritional supplement comprising approximately from about 10 to about 75 grams carbohydrate; approximately from about 5 to about 50 grams protein; approximately from about 3 to about 30 grams fat comprising at least two different fat sources of which one is oil rich in monounsaturated fatty acids and the other is oil rich in omega-3 fatty acids; and therapeutic amounts of antioxidant.

27. The method of claim 26, wherein the carbohydrate comprises sucrose, maltodextrin, corn starch; canola oil, whey protein, fish oil, vegetable oil, dairy fat and medium-chain triglycerides.

28. A method of reducing postoperative infections in a surgical patient comprising administering to the patient the nutritional supplement of claim 1, for a sufficient period of time prior to surgery.

29. A method of preventing weight loss and/or malnutrition in a patient in imminent need of surgery, comprising administering to the patient the nutritional supplement of claim 1, for a sufficient period of time prior to surgery.

30. A method of improving the nutritional status of a patient in imminent need of surgery, comprising administering to the patient the nutritional supplement of claim 1, for a sufficient period of time prior to surgery.

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L1: Entry 6 of 6 File: USPT Aug 1, 1989

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TITLE: Method and composition for increasing production of serotonin

DATE-ISSUED: August 1, 1989

INVENTOR-INFORMATION:

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This application is a continuation of application Ser. No. 025,002, filed Mar. 12, 1987, now abandoned, which is a continuation-in-part application of application Ser. No. 787,502, filed Oct. 15, 1985, now U.S. Pat. No. 4,650,789.

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ABSTRACT:

The production of the neurotransmitter serotonin is increased through administration of a therapeutic composition which includes L-tryptophan in combination with a salicylate, an ascorbate, calcium, magnesium, copper, pyridoxine, niacin and a carbohydrate such as fructose. Both the absolute free fraction and the relative amount of the albumin-bound fraction of serum L-tryptophan are increased so that transport of L-tryptophan from the blood plasma across the blood-brain barrier into the brain is increased. Once within the brain, L-tryptophan is converted to serotonin.

13 Claims, 0 Drawing figures
Exemplary Claim Number: 1

BRIEF SUMMARY:

1 Reference is made to the co-pending patent application of Robert L. Pollack and Lawrence Durst, application Ser. No. 007,121, filed Jan. 26, 1987 and to U.S. Pat. No. 4,639,465, of Robert L. Pollack and Lawrence Durst, issued Jan. 27, 1987.

2 BACKGROUND OF THE INVENTION

3 1. Field of the Invention

4 This invention relates generally to a dietary supplement for relieving physiological disorders and particularly relates to a composition which promotes the production of serotonin within the brain.

5 2. Description of Prior Developments

6 Attention has recently turned to nontraditional methods and compositions for treating various physiological disorders in an effort to provide relief in those instances where standard techniques have proven ineffective and where it is desired to avoid the undesirable side effects of conventional pharmaceutical compositions. One approach has been to attempt to provide relief through dietary supplementation of L-tryptophan (tryptophan).

7 Once within the brain, neurons convert tryptophan into the neurotransmitter serotonin. It has been found that an increase of tryptophan in the brain increases the brain's production of serotonin. Brain levels of serotonin have been shown to be linked to sleep, appetite, depression, and pain threshold. Disturbances in the brain causing reduced levels of serotonin have been linked to clinical (endogenous) depression, insomnia, excessive appetite, weight gain and lowered pain threshold.

8 While treatment of such disorders with supplemental tryptophan has heretofore produced positive results, there has been a wide range in the degree of relief achieved. Some patients appear to respond more favorably to such treatment than others for no previously known reason. Thus, complete relief has not consistently been assured by prior dietary tryptophan supplements. It is believed that these conventional supplements lack a complete combination of ingredients necessary to ensure the maximum relief achievable with every patient through tryptophan supplementation.

9 It is known that dietary supplementation of tryptophan increases the blood level of tryptophan and facilitates the passage of tryptophan across the blood-brain barrier into the brain. The increased amount of tryptophan in the brain permits a greater amount of tryptophan to be converted to serotonin.

10 In order for tryptophan to be converted to serotonin in the brain, it must cross a separating mechanism that exists between the blood vessels and the brain. To reach the brain, tryptophan requires a carrier transport mechanism in the form of a carrier protein which, literally, carries tryptophan across this very selective blood-brain barrier and into the brain. Not only is tryptophan carried by this transport mechanism, but other selected amino acids, called large neutral amino acids (LNAAs), are carried as well.

11 Tryptophan not only has to compete with the LNAAs for access to the transport carrier mechanism, it also has a lower affinity for the carrier system than does the LNAAs. To compound this situation further, tryptophan in foods is generally present in lower amounts than the LNAAs--particularly in animal proteins. All of these factors contribute to the amount of tryptophan that actually gets through to the brain, to be finally converted to serotonin.

12 There are numerous conditions, improper diet constitutes one of them, that can interfere with, and decrease, the amount of tryptophan that normally passes through the blood-brain barrier into the brain each day. This comes about when the ratio of tryptophan to LNAAs in the blood reaching the brain is lower than normal. This means that the number of molecules of tryptophan present at the blood-brain barrier is much smaller than the number of molecules of LNAAs

present at the same blood-brain barrier. The LNAAs overwhelm the tryptophan such that very little tryptophan is provided passage into the brain as compared to the number of LNAAs that are provided passage.

13 In the attempt to correct this improper tryptophan/LNAA ratio, it was found that increasing the total protein intake obtained from normal dietary sources, in order to add more tryptophan to the system, results, paradoxically, in an even greater decrease in the amount of tryptophan reaching the brain. This is so because there are usually more LNAAs than there is tryptophan in food. Experimental studies have established the fact that increasing the amount of protein as food, in order to improve the tryptophan/LNAA ratio, only makes the tryptophan/LNAA ratio worse because of the greater intake of the LNAAs over the intake of the tryptophan.

14 With less tryptophan getting into the brain, less serotonin is formed, and a wide variety of disorders, including those noted above, begin to manifest themselves. Because these disorders stem from a biochemical imbalance involving the tryptophan-serotonin relationship, they cannot be corrected by any conventional medication. Such disorders are unmanageable by any conventional drug therapy because the drug does not address itself to the correction of this specific biochemical imbalance.

15 Accordingly, a need exists for a method and composition for transporting an effective dose of tryptophan across the blood-brain barrier into the brain and for promoting the conversion of tryptophan into serotonin. Moreover, a need exists for a composition which provides all the ingredients necessary to achieve the maximum relief possible through dietary supplementation of tryptophan.

16 SUMMARY OF THE INVENTION

17 The present invention has been designed as a dietary therapeutic composition including a combination of ingredients which will provide the proper and effective dietary supplementation of both free and albumin-bound tryptophan for increasing the production of serotonin in the brain. Increased serotonin production can decrease or eliminate chronic pain, particularly in those conditions where the pain stems from an unknown origin, and not due to any known medical, dental or psychological reason. Moreover, clinical depression, insomnia and appetite disorders may also be relieved or eliminated via such dietary supplementation.

18 The administration of pure tryptophan will help to improve the ratio of blood tryptophan to blood LNAAs, help to increase the amount of tryptophan that will enter the brain, and help to increase the serotonin level within the brain and raise the pain threshold level while concurrently relieving depression, insomnia and certain appetite-related disorders. The effectiveness of pure tryptophan in raising the pain threshold level and in relieving depression, insomnia and other disorders including excessive appetite can be improved with the addition of other specific dietary supplements as set forth below.

19 The oral administration of tryptophan in combination with several other operative ingredients taken under proper dietary conditions provides a supplementary intake of this particular amino acid which helps to correct an improper tryptophan/LNAA ratio. The dietary supplementation of the tryptophan-based composition described below, combined with an adjusted protein, low fat, higher carbohydrate intake, results in a significant reduction in any one or all unpleasant symptoms experienced by patients having low or insufficient brain levels of serotonin. When administered as an anorectic, the composition significantly reduces intake of all calorie laden nutrients including protein, fats and carbohydrates, thereby serving as an effective aid in any weight control program.

20 L-tryptophan is usually not transported in the blood in a free state, but rather in a bound or complexed form with the protein albumin, a plasma component. In fact, L-tryptophan is the only circulating amino acid that is significantly bound to human serum albumin. It has been shown that various salicylates

displace tryptophan from its protein binding site with albumin in blood plasma thereby raising the free or unbound tryptophan concentration in the blood. The bond-breaking effect exerted by salicylates on the binding of tryptophan to albumin causes a greater availability of free tryptophan molecules for diffusion into body cells.

21 In humans, the ingestion of salicylates such as magnesium salicylate and aspirin causes a release of tryptophan from its binding site on serum albumin, and results in the presence of a free, unbound fraction of tryptophan within the blood. It has now been determined that it is primarily the free fraction of serum tryptophan which controls the concentration of brain tryptophan as well as the brain's production of serotonin. The greater the amount of the free or unbound tryptophan, the greater the amount of serotonin production.

22 The brain tryptophan level reflects brain serotonin turnover so that the resultant increase in the availability of circulating free tryptophan to the brain leads to an enhancement of brain serotonin synthesis.

23 A major aspect of the present invention is specifically directed to the addition of a salicylate, calcium, magnesium and ascorbic acid to a tryptophan-based composition so that both the level of serotonin within the brain is increased and the quality and strength of the nerve signals or impulses transmitted by this neurotransmitter is improved and strengthened.

24 In order to appreciate the specific selection and combination of ingredients described below, a brief description of the biochemical processes by which tryptophan is converted into serotonin is of value.

25 Generally, serotonin is produced within brain membranes by a process involving the interaction of the amino acid L-tryptophan with the enzyme tryptophan hydroxylase. More particularly, two separate enzymatic steps are necessary for the synthesis of serotonin (5-HT) from its natural precursor tryptophan. The first step involves the conversion of tryptophan into 5-hydroxytryptophan (5-HTP) via interaction with the enzyme tryptophan hydroxylase. The second step involves the decarboxylation of 5-HTP into 5-HT via aromatic amino acid decarboxylase.

26 It is the first step which is believed to present the greatest hurdle in the conversion of tryptophan to serotonin. Moreover, it is believed that this first step primarily affects the amount of serotonin produced within the brain. Accordingly, it is the first enzymatic step on which the present invention concentrates.

27 As stated, tryptophan must first be converted to 5-HTP by tryptophan hydroxylase. However, only a special activated form of tryptophan hydroxylase will bring about this conversion. This activated form is a phosphorylated form of tryptophan hydroxylase which is produced through the action of a calcium-dependent protein kinase. It is calcium which stimulates the kinase to posphorylate the tryptophan hydroxylase. Thus, the addition of calcium to the tryptophan composition ensures the adequate presence of calcium required to initiate the conversion of tryptophan to serotonin.

28 Another factor in the synthesis or conversion of tryptophan into serotonin involves the hydroxylation of tryptophan by the phosphorylated tryptophan hydroxylase. The rate-limiting step in the synthesis of serotonin is the hydroxylation step which is catalyzed by tryptophan hydroxylase. Once tryptophan crosses the blood-brain barrier into the brain, the tryptophan bonds with nerve membranes on serotoninergic neurons. At this point the tryptophan undergoes hydroxylation by accepting an OH group from the activated enzyme tryptophan hydroxylase, a copper-protein enzyme, which is present within the brain.

29 The hydroxylation of tryptophan is believed to involve the reduction of the calcium/kinase-activated tryptophan hydroxylase copper atoms and the reduction of a presently unknown enzyme group X also present on the enzyme. Thus, by providing supplemental ascorbic acid and copper according to the invention, the

hydroxylation of tryptophan into 5-HTP is further facilitated. The reduction of the tryptophan hydroxylase takes place by the successive addition of single electrons to its copper atoms and to the enzyme group X from ascorbic acid. That is, tryptophan hydroxylase is a copper-protein complex that uses ascorbic acid as a reducing agent. Thus, by providing supplemental ascorbic acid and copper according to the invention, the hydroxylation of tryptophan into 5-HTP is further facilitated.

30 In short, calcium initially stimulates kinase to activate (phosphorylate) tryptophan hydroxylase. The tryptophan is then hydroxylated by the activated or phosphorylated tryptophan hydroxylase through reduction of copper via electron transfers from ascorbic acid.

31 To further ensure the efficacy of serotonin in relieving physiological disorders, magnesium is added to the composition, preferably along with calcium, to increase the bond strength between serotonin and the nerve membranes as well as to increase the total number of binding sites available to serotonin on the brain/nerve membranes. By increasing both the strength and the number of bonds between serotonin and the nerve membranes, a stronger nerve impulse or signal is transmitted by the passage of serotonin across the nerve synapses thereby resulting in a more pronounced physiological effect leading to more pronounced relief.

32 It is possible that the somewhat unpredictable results achieved by prior tryptophan-based compositions may be attributable to a lack of ascorbic acid, calcium and/or magnesium available in the patient's brain for the conversion of tryptophan to serotonin.

33 It is therefore an object of the invention to povide a method and composition for relieving physiological disorders through dietary supplementation of tryptophan in combination with other ingredients which facilitate the brain's synthesis of serotonin.

34 Another object is to efficiently transport tryptophan across the blood-brain barrier so that an effective relief-yielding quantity of serotonin is produced within the brain.

35 Still another object of the invention is to provide a method and composition for promoting the conversion of tryptophan to serotonin within the brain.

36 Yet another object is to facilitate the activation of the enzyme tryptophan hydroxylase which, when activated, converts tryptophan into a precursor of serotonin, namely, 5-hydroxytryptophan.

37 Still another object is to increase the total number of available serotonin binding sites on brain membranes.

38 Another object is to increase the specific binding of serotonin to all available binding sites on brain membranes by increasing the bond strength between serotonin and nerve axons.

39 Yet another object is to provide a method and composition for relieving pain, depression, excessive appetite and insomnia by triggering the release or displacement of tryptophan from its usual protein-bound or complexed state within the blood plasma to a free, unbound state in order to increase the free tryptophan concentration in blood.

40 A further object is to increase both the bound and unbound (or complexed) fraction of tryptophan within blood plasma in order to maximize the amount of tryptophan transported across the blood-brain barrier into the brain for production of serotonin.

41 A particularly effective composition has been found to include tryptophan, a salicylate such as acetylsalicylic acid (aspirin) or magnesium salicylate, calcium, magnesium, ascorbic acid, copper, niacinamide, pyridoxine, and a

carbohydrate such as a sugar. A most effective sugar has been found to be fructose, which yields a steadily metered release of insulin into the blood. A preferred single source of both calcium and ascorbic acid is available as calcium ascorbate and a preferred single source of both a salicylate and magnesium is available as magnesium salicylate.

42 Various other objects, features and attendant advantages of the present invention will be more fully appreciated as the same becomes better understood from the following detailed description.

DETAILED DESCRIPTION:

1 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

2 As briefly stated above, there are up to nine operative ingredients which, when combined according to the invention, yield an effective composition for promoting the transport of tryptophan from the blood plasma into the brain and for promoting the synthesis of serotonin from tryptophan within the brain. High brain levels of serotonin have been shown to increase one's pain threshold level, decrease appetite, relieve depression and promote sleep. The primary ingredient, tryptophan, may be provided in any amount ranging from about 50 milligrams per dosage up to about 12 grams per dosage. However, a preferred dosage range has been found to extend from about 50 milligrams to one gram per dosage, particularly if the dosage is repeated several times daily. A preferred dosage schedule during waking hours may range from once an hour to once every three or four hours.

3 In addition to the primary ingredient tryptophan, any one, several or all of the following eight types of additional ingredients may be provided to facilitate tryptophan transport into the brain and/or to promote conversion of tryptophan into serotonin. These additional ingredients may either be directly combined with tryptophan and formed as a tablet or capsule, or may be coadministered as separate ingredients. Preferably, the dosage schedule of each additional ingredient would be the same as that for the tryptophan.

4 The first supplemental ingredient is calcium, preferably in the form of calcium ascorbate provided in single dosage amounts ranging from 1 to 500 milligrams. Calcium may alternatively be supplementally provided as any one or any combination of the following salts of calcium within a single dosage weight range of 1 to 500 milligrams:

calcium ascorbate	calcium gluconate
calcium carbaspirin	calcium glycerophosphate
calcium carbonate	calcium lactate
calcium caseinate	calcium pantothenate
calcium chloride	dicalcium phosphate
calcium glubionate	tricalcium phosphate
	calcium pyrophosphate

5 A most effective dosage for the above-listed salts may vary from 10 to 100 milligrams.

6 When a nerve cell is stimulated, one of the first events to occur is a transient

but significant increase in free intracellular calcium concentrations. Concentrations of calcium also increase in the nerve cell endings upon transmission of a nerve impulse. Calcium migrates from within the neuron fibers to the outer surfaces of the cell upon nerve stimulation thereby raising the concentration of calcium at the nerve endings. This increase in calcium signals the nerve cell to release the nerve's chemical transmitter, i.e., serotonin.

7 Calcium does not act alone in triggering the release of serotonin. Rather, calcium stimulates the release of neurotransmitters in concert with the protein calmodulin. Calmodulin acts as an intracellular intermediary or regulator for calcium ions. As noted above, an activated form of kinase is required for the synthesis of serotonin. The calcium ions activate kinase by combining with calmodulin on serotoninergic neurons to form a calcium-calmodulin complex. Without sufficient calcium, the transmission of the nerve impulses is impeded since insufficient kinase is activated.

8 Calcium not only plays a crucial role in the depolarization-induced activation of tryptophan hydroxylase as previously discussed, but also aids the binding of serotonin to nerve membranes. Whereas high concentrations of monovalent cations (greater than 20 mM of Na or K) induce a significant inhibition of serotonin binding to brain membranes, millimolar concentrations of divalent cations such as calcium (Ca.sup.2) and magnesium (Mg.sup.2) consistently increase the specific binding of serotonin to nerve cells responsible for transmission of nerve impulses. In addition, calcium also increases the total number of available specific binding sites for serotonin in brain membranes.

9 Accordingly, a calcium "window" exists between upper and lower limits of calcium concentrations wherein sufficient calcium is provided to activate kinase but not in excessive amounts which would inhibit the binding of serotonin on nerve membranes. By providing 1 to 500 milligrams of a calcium salt as specified, calcium concentrations will be maintained within this "window" range.

10 Another ingredient which is advantageously included in the supplemental dietary composition is a magnesium supplement, preferably in the form of magnesium salicylate in amounts ranging from 1 to 500 milligrams. Magnesium may also be provided as any one or any combination of the following salts of magnesium within a weight range of 1 to 500 milligrams:

magnesium carbonate	magnesium oxide
magnesium gluconate	magnesium salicylate
magnesium hydroxide	magnesium sulfate
	magnesium trisilicate

11 These salts are preferably administered in amounts ranging from 10 to 100 milligrams per dosage.

12 Nerve impulses are transmitted across the nerve synapse under the control of an on-off switching mechanism. The "on" state is energized by the production of various neurotransmitters including serotonin. Serotonin is produced in the nerve dendrites and travels across the synapse to the axon of an adjacent nerve cell. In order to effectively transmit the nerve signal from one nerve cell to another, serotonin must find a binding site on an adjacent axon. The presence of millimolar concentrations of magnesium not only increases the number of available binding sites for serotonin but also increases the strength of the resulting bonds between the neurotransmitters and the nerve cells. The result is a stronger and clearer transmission of nerve signals via enhanced transmission and binding of serotonin. This in turn results in more effective relief of the

disorders associated with a tryptophan deficiency.

13 Ascorbic acid is another ingredient which is beneficial for promoting production of serotonin. Ascorbic acid is a hydrolase cofactor which is required for the hydroxylation of L-tryptophan to 5-hydroxytryptophan as outlined above. A preferred form or compound for supplemental ascorbic acid is calcium ascorbate which, when ingested, provides not only ascorbic acid but also the calcium required to initiate the phosphorylation of tryptophan hydroxylase. The weight range of the calcium ascorbate is preferably within 1 to 500 milligrams. Other suitable sources of ascorbic acid include:

14 sodium ascorbate

15 calcium ascorbate

16 niacinamide ascorbate

17 These alternate sources of ascorbic acid should be maintained within the 1 to 500 milligram limit specified above with a preferred range of 10 to 100 milligrams per dose.

18 Another ingredient which is beneficial in optimizing the production of serotonin is copper, the mineral element that serves as a co-factor in the enzymatic reaction involving tryptophan hydroxylase. A copper supplement will therefore facilitate the conversion of tryptophan into serotonin. A preferred form or compound for supplemental copper is copper gluconate which, when ingested, provides the element copper which is essential in the formation of the active enzyme complex. The weight range of the copper dosage is preferably within 0.1 to 100 milligrams. Other suitable sources of copper include:

19 copper sulfate

20 amino acid chelates of copper

21 The preferred dosage forms of these salts are in amounts of copper ranging from 0.1 to 100 milligrams of copper.

22 Niacinamide is another additional ingredient which may be included to promote or facilitate tryptophan transport into the brain. Niacin is an essential nutrient that the human body must have at all times. Because of niacin's importance, the body has evolved a method by which it can synthesize niacin from tryptophan. More particularly, 60 milligrams of tryptophan is used by the body to make each milligram of niacin. Studies in humans have shown that the amount of niacin the body gets from tryptophan amounts to about one-half of the total amount of niacin that the body needs each day, that is, about 13-19 mg. This means that from (13/2.times.60) mg to (19/2.times.60) mg or 390 mg to 570 mg of tryptophan is needed each day for its conversion to niacin.

23 In order to attempt to minimize the destruction of the supplemental tryptophan within the body via synthesis into niacin, a niacin supplement such as niacinamide or nicotinamide is included along with the tryptophan to provide the body with the pre-formed vitamin niacin. Furthermore, it has been learned that some of the beneficial effects of tryptophan in raising brain levels of serotonin may be diminished by a rapid breakdown (catabolism) by tryptophan pyrrolase. The administration of a tryptophan pyrrolase inhibitor such as niacinamide, nicotinamide or nicotinic acid inhibits such tryptophan breakdown in man. A practical dosage may range from 1 milligram to 100 milligrams with a preferred range of 5 to 25 milligrams.

24 The next operative ingredient of the invention is pyridoxine (vitamin B.sub.6). Pyridoxine is essential in the tryptophan-serotonin conversion process and is part of the enzyme system which functions directly in the conversion of tryptophan to serotonin. That is, pyridoxine is a decarboxylase co-factor required for the decarboxylation of 5-hydroxytryptophan to serotonin. By providing the body with this vitamin at the same time that the supplemental

tryptophan is administered, this important nutrient will be provided to individuals whose dietary intake may have been deficient. This will ensure efficient conversion of tryptophan to serotonin. Pyridoxine may be administered in dosages ranging from 0.5 to 50 milligrams, with a preferred range of 1 to 10 milligrams per dose.

25 The next ingredient is a carbohydrate such as a sugar, preferably the monosaccharide sugar, fructose. Investigations have shown that dietary carbohydrate causes an increase in the relative concentration of blood tryptophan levels; i.e., the amount of tryptophan is increased relative to the amount of the interfering large neutral amino acids that compete with tryptophan for the transport carrier mechanism in the brain. Of all the blood amino acids, tryptophan is the only amino acid that is carried as an albumin-bound complex. All of the other amino acids, including the LNAAs, travel in the blood as the free amino acids.

26 Insulin, when elaborated into the blood stream in response to an increase in blood sugar concentration serves to drive amino acids into the body tissues while the blood courses on its way to the brain. The tryptophan-albumin complex is not affected by this insulin action, and thus remains available to reach the brain. Thus, this complex is not "lost" to the body tissues. However, the other amino acids are removed from the blood thereby increasing the relative percentage of tryptophan in the blood. Carbohydrate intake, therefore, with its insulin-releasing action, helps to improve the tryptophan/LNAA ratio in favor of the tryptophan and increases the amount of tryptophan crossing the blood-brain barrier into the brain. Fructose is included in each capsule as a preferred source of carbohydrate to achieve this insulin/LNAA/tryptophan effect.

27 Relatively modest dosages of fructose have been found sufficient to produce the desired effects. For example, dosages of fructose as little as 5 milligrams have been found to increase the effect of tryptophan in providing relief of the disorders mentioned above. A preferred dosage ranges from 25 milligrams to one gram per dosage.

28 The next, but crucial, ingredient is a salicylate, preferably an oral salicylate salt. As previously noted, tryptophan is usually not transported in the blood in a free state, but rather in a bound or complexed form with the protein albumin, a plasma component. Tryptophan is the only circulating amino acid that is significantly bound to human serum albumin. It has been shown that salicylates displace tryptophan from its protein binding site on albumin in blood plasma thereby raising the free, circulating tryptophan concentration in blood. This free or unbound tryptophan is more easily converted to serotonin than the bound form and therefore its presence is most desired.

29 While it may seem paradoxical to release tryptophan from its complexed state with albumin through administration of a salicylate, then to drive the resulting free tryptophan into the body tissues along with the other free amino acids via administration of a carbohydrate and release of insulin, the end result of this action is an overall increase in the transport of tryptophan into the brain. The exact interaction in this case is not completely known, although the combination of the free tryptophan provided by oral administration of the composition and the free tryptophan released from serum albumin may not collectively enter the body tissues under the influence of insulin to the extent or relative percent that the other free amino acids do, thereby increasing the relative serum concentration of free tryptophan.

30 Moreover, since not all of the serum tryptophan is released by the salicylate from its bound state, the remaining albuminbound tryptophan is allowed to reach the brain at which point it is freed from albumin and transported into the brain by the body's own release mechanism. Thus, the combined effect of the administration of a salicylate and a carbohydrate along with free tryptophan is to increase both the absolute free fraction of circulating tryptophan and the relative amount of albumin-bound tryptophan in relation to the remaining LNAAs.

31 A particularly effective method of administration is to delay the

tryptophan-releasing action of the salicylate until the insulin released by the carbohydrate, preferably fructose, has driven the LNAAs into the body tissues. A further advantage may be gained by delaying the administration of tryptophan until the presence of the LNAAs within the blood is decreased by the action of the insulin. This can be achieved by first administering the carbohydrate, waiting about five minutes to an hour for the insulin to reduce the concentration of LNAAs within the plasma, then administering the salicylate, tryptophan and any desired additional ingredients. The advantage gained is that the albumin-bound tryptophan will not be freed prior to the release of insulin so that the bound tryptophan will remain in the blood while the LNAAs are removed from the blood. By administering the salicylate after the carbohydrate, the tryptophan freed from the albumin will not be lost to the body tissues under the action of insulin, but will remain in the blood for transport into the brain. Moreover, by delaying the administration of supplemental tryptophan until at least five minutes after the administration of a carbohydrate, the supplemental tryptophan will not be driven into the body tissues so that the concentration of serum tryptophan may be maximized.

32 An alternate method of delaying the administration of the salicylate and/or the tryptophan is to microencapsulate the salicylate and/or the tryptophan by conventional processes to achieve a timed delay of these ingredients into the blood. In this manner, all ingredients may be taken orally at the same time for convenience, yet the bound and supplemental tryptophan will be protected from the initial action of the insulin.

33 It should be emphasized that a salicylate such as aspirin may be used according to the invention solely for its ability to safely break the bond between tryptophan and albumin in order to increase the free fraction of serum tryptophan and not for the well-known analgesic effect produced by salicylates. In fact, any salicylate administered alone in the dosages set forth below (without the additional ingredients) will not lower the threshold of pain to any degree near that when combined with any combination of or all of the ingredients identified herein.

34 While magnesium salicylate is the pharmaceutical agent presently preferred to effect release of tryptophan from its bound or complexed state with albumin, any other pharmaceutically acceptable oral salicylate salt such as sodium salicylate, choline salicylate or any other substance which safely produces this release would serve as well. For example, acetanilid, acetophenetidin, and aminopyrine could be used in about the same dosage as aspirin to achieve the same result. Other pharmaceutically acceptable substances have been found capable of releasing tryptophan from serum albumin and could be combined with tryptophan and the other ingredients in addition to or in place of a salicylate so as to fulfill the goal of the present invention. Such substances include heparin, isoprenaline, aminophylline, dopa, clofibrate, unesterified fatty acids, probenecid, bulbocapnine, and acetaminophen.

35 A particularly effective and convenient source of both magnesium and a salicylate has been found to be magnesium salicylate. This salicylate salt is generally preferred over aspirin because magnesium salicylate does not act as an anticoagulant. That is, salicylate salts do not inhibit platelet aggregation and therefore do not add an additional active agent to those patients already receiving anticoagulant medication.

36 The effective dosage of magnesium salicylate may range from 1 to 500 milligrams with a preferred dosage range of 10 to 200 milligrams. Choline salicylate or sodium salicylate may be substituted for magnesium salicylate in about the same dosage or dosage ranges as specified for magnesium salicylate.

37 While the weight percentages of each ingredient listed below could vary at least by 50% and in accordance with the amounts found to achieve an optimum effect, a preferred composition of the supplement for an effective pharmaceutically acceptable single dosage (tablet or capsule) for a typical patient is approximately as follows:

	Weight in mg	% by weight (approx.)
L-tryptophan	200	43.0
Fructose	125	26.9
Niacinamide	10	2.1
Pyridoxine	5	1.1
Calcium ascorbate	55	11.8
Magnesium salicylate	55	11.8
Copper gluconate	15	3.2
Total weight of tablet	465 mg	100%

38 Because the above composition can be taken orally in amounts up to 10-12 capsules daily, the inclusion of the sugar, fructose, was deliberately selected rather than glucose or sucrose because of studies which indicate that the response of the body in releasing insulin into the blood is much more even with fructose than with the other sugars that were used and without any sudden insulin upsurge. Thus, fructose provides the desired predictability of insulin release needed for a constant production of serotonin which in turn is required for the satisfactory even relief of physiological disorders.

39 Treatment of physiological disorders may be carried out according to the invention with maximum sustained or prolonged daily dosages of up to:

L-tryptophan	15	grams
Fructose	20	grams
Niacinamide (Nicotinamide, Nicotinic Acid)	2	grams
Pyridoxine	2	grams
Calcium ascorbate (or any other calcium salt)	6	grams
Magnesium salicylate (or any other magnesium salt)	6	grams
Ascorbic Acid (or any other acceptable ascorbate)	6	grams
Copper gluconate (or any other copper salt)	1	gram
Acetylsalicylic acid (or any other oral salicylate)	4	grams

40 These maximum dosages may be administered at one time and in any combination which includes at least L-tryptophan, a salicylate and fructose, although lesser dosages spaced over time are preferred.

41 Obviously numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein. For example, other carbohydrates could be used in place of fructose without departing from the spirit of the invention.

42 While upper daily limits have been placed on each ingredient for prolonged use of the composition, virtually no upper limit need be maintained for any ingredient for initial or intermittent treatment of physiological disorders. It has been found that initial treatment may require five to ten times the maximum normal or sustained dosages identified above in order to accelerate initial relief. Once relief is achieved, lower dosages may be maintained according to the above-specified ranges.

43 Moreover, it should be noted that only tryptophan, an oral salicylate, and fructose are essential to carry out the invention. The remaining ingredients are optional and may be added in any combination with the tryptophan, salicylate and fructose depending upon the dietary deficiency of a particular patient. Those patients exhibiting a deficiency in any one or a combination of the remaining ingredients may be treated only with those ingredients specifically required to overcome the patient's particular deficiency.

CLAIMS:

What is claimed is:

1. A method for treating physiological disorders responsive to treatment with L-tryptophan, wherein said method comprises:

administering to a patient a dosage of a composition comprising L-tryptophan in an amount sufficient to increase transport of L-tryptophan into the patient's brain and a salicylate selected from the group consisting of sodium salicylate, choline salicylate and magnesium salicylate in an amount sufficient to release L-tryptophan from the patient's serium albumin, said dosage of the composition being sufficient to increase production of serotonin within the patient's brain to a level which provides relief of said physiological disorders.

2. The method of claim 1, which further comprises administering to the patient a dosage of a carbohydrate.

3. The method of claim 1, which further comprises administering to the patient a dosage of a carbohydrate, a dosage of a calcium supplement, a dosage of a magnesium supplement, a dosage of an ascorbate, a dosage of a copper supplement, a dosage of a niacin supplement and a dosage of pyridoxine.

4. A composition for increasing production of serotonin within a patient's brain, comprising a dosage of L-tryptophan in an amount sufficient to increase transport of L-tryptophan into the patient's brain, and

a dosage of a pharmaceutically acceptable salicylate, selected from the group consisting of sodium salicylate, choline salicylate and magnesium salicylate said dosage of said salicylate being sufficient to release L-tryptophan from the patient's serum albumin, and

said dosages combined so as to increase said production of serotonin to a level which provides relief of physiological disorders.

5. The composition of claim 4, further comprising a dosage of a carbohydrate in an amount sufficient to release insulin into the patient's blood for freeing albumin-bound L-tryptophan.

6. The composition of claim 4, further comprising a dosage of a calcium supplement for facilitating conversion of L-tryptophan into serotonin.

7. The composition of claim 4, further comprising a dosage of a magnesium supplement for enhancing the neurotransmission of serotonin.

8. The composition of claim 7, wherein said salicylate and said magnesium supplement are each provided in the form of magnesium salicylate.

9. The composition of claim 4, further comprising a dosage of ascorbic acid for

facilitating hydroxylation of L-tryptophan.

10. The composition of claim 9, wherein said ascorbic acid is provided as an ascorbate selected from the group consisting of sodium ascorbate, calcium ascorbate and niacinamide ascorbate.

11. The composition of claim 4, further comprising a dosage of a copper supplement for facilitating conversion of L-tryptophan into serotonin.

12. The composition of claim 4, futher comprising a dosage of a niacin supplement for preventing synthesis of niacin from L-tryptophan.

13. The composition of claim 4, further comprising a dosage of pyridoxine for facilitating conversion of L-tryptophan into serotonin.